
The combined effect of SR4233 (Tirapazamine®) and FMdC on radiation sensitivity in vitro and in vivo: is this effect linked to inhibition of angiogenesis?

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Purpose: To investigate in vitro and in vivo the association of SR4233, FMdC and irradiation on a WiDr colon cancer cell line and xenograft model. To determine the effect of FMdC and SR4233 on VEGF by RT-PCR and Western blot.
Materials and methods: Clonogenic assays in oxygenated and hypoxic conditions to test radiosensitizing capacity of FMdC and/or SR4233. Xenografts of WiDr implanted in Swiss nude mice to test the effect on growth delay after irradiation. Semi-quantitative investigation of VEGF-mRNA by RT-PCR and VEGF protein by western blotting in vitro on ECV cell line.
Results: In anoxic conditions FMdC looses it's radiosensitizing effect in vitro. The combined effect of FMdC and SR4233 results in major increase of radiosenistivity of WiDr cells in hypoxic conditions compared to FMdC alone. In vivo, the post-irradiation growth delay increases significantly by using the combination FMdC and SR4233 as compared to each compound alone. The evaluation of the effects of FMdC and SR4233 on the VEGF-mRNA and VEGF protein are currently under investigation on a human endothelial cell line (ECV), and data will be presented at the meeting.
Conclusion: FMdC looses it's capacity to sensitize WiDr cells in anoxic conditions; however, in these hypoxic conditions the combination of FMdC and SR4233 results in significant increase of radiation induced cell kill, highlighting the potential of combining a compound with anti-angiogenic effects to a biorecductive drug.